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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/554,465 | 10/19/2000 | Peter Kufer | 147-199P | 3425 |

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| EXAMINER | |
|---|---|
| CHEU, CHANGHWA J | |
| **ART UNIT** | **PAPER NUMBER** |
| 1641 | |

DATE MAILED: 04/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/554,465 | KUFER ET AL. | |
| | Examiner | Art Unit | |
| | Jacob Cheu | 1641 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's amendment filed on 11/8/2005 has been received and entered into record and considered.

The following information provided in the amendment affects the instant application:

1. Claim 1 is added to the instant application.
2. Claim 1-36 are under examination.

### *Specification*

The specification is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (i.e. see page 17, line 1-10). Applicant is requested to delete all embedded hyperlinks and/or other form of browser-executable codes. See MPEP § 608.01

1. Claim 21 and 27 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claims. See MPEP § 608.01(n).

### *Claim Rejections - 35 USC § 112*

### *Enablement*

### *CDR Binding Region*

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 22-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in

the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As set forth in *In re Wands, 858 F .2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)*, enablement requires that the specification teach those skilled in the art to make and use the invention without undue experimentation. Factors to be considered in determining, whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The instant invention directs to a method of identifying at least one epitope binding domain capable of binding to a predetermined epitope. The said method comprise using phage library display system having a N-terminal block domain linked to $V_H$-$V_L$ (recombinant polypeptide) connecting its C-terminal to an anchoring CT domain in identifying potential binding domain on the $V_H$-$V_L$.

It is noted that applicant recites the binding domain comprises at least one CDR of the scFv fragment according to ***ANY ONE*** of the SEQ ID No. 61, 63, 65, 67, 69, 71, 73, 75 and 77 (emphasis added). Such a recitation would impose enablement problem under *In re Wands* ruling.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. (See Paul, Fundamental Immunology, (textbook), 1999, under the heading "Immunoglobulins: Structure and Function, , pp. 37, 43, 58, 59; Janeway et al. eds. Immunobiology, third edition, section 3-6

and 3-7). It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that fusion proteins as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an IL-1ß antibody in unspecified order and fused to any human or nonhuman framework sequence, have the required binding function.

Furthermore, the above information is reiterated by applicant in the specification *"it is in this CDRs of each variable domain interact to define an antigen binding site on the surface of the $V_H$-$V_L$ dimer. Collectively, the* ***six CDRs confer antigen binding specificity*** *to the antibody* "(See page 5, last paragraph)(emphasis added). The specification provides no direction or guidance, or example of any one of the recited CDR could ALONE act/or operate as an antigen binding domain. In view of the aforementioned lack of predictability in the art, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in the applicant's specification of how to effectively practice the recited method and absent working examples.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 1-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With respect to claim 1, step (a), it is not clear what is the "N-terminal blocking domain". Particularly, it is not clear what "blocking" applicant refers to. Similarly, the same terms are used throughout the remaining claim language.

With respect to claim 9, it is not clear whether this "C-terminal domain" should be "N-terminal domain" since it is the N2-domain from the gene III product of filamentous phage (See page 7, last paragraph; page 8, line 15-25). Applicant needs to clarify.

***Response to Applicant's Arguments***

6. The rejections of claims 1-8, 10-11, and 19-21 under USC 35 103 (a) as unpatentable over Holliger et al. in view of Barbas et al. are withdrawn.

7. For patentably distinct SEQ ID No. 61, 63, 65, 67, 69, 71, 73, 77, applicant argues that no such statement has been made by applicant. Examiner acknowledges applicant's statement. However, in view of enablement issue, examiner establishes the requirement of CDR binding region for the necessary polypeptide, not ANY ONE of the SEQ ID ALONE, is enable (See this Office Action).

8. With respect to Finality, examiner indicated that the rejection is based on the amendment necessitated the new ground(s) of rejection (See Final rejection). Nevertheless, the issue has been moot by this Non-Final Office Action.

9. With respect to improper prior art indicating allowable subject matter, examiner agrees and cites another closest prior art for the reasoning of allowance (See Below).

***Allowable Subject Matter***

10. Claim 1-21 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action.

11. The following is an examiner's statement of reasons for allowance: no prior art teaches or fairly suggests identifying at least one epitope binding domain by coupling an additional domain

at the N-terminus of a panel of recombinant polypeptides, and an anchoring domain at the C-terminus of the said recombinant polypeptidesto where the epitope binding domain is located between the N-terminus domain and C-terminus anchoring domain. The closest prior art is the teachings of Krebber et al. (FEBS 1995, vol. 377, page 227) where Krebber et al. teach using a phage library to identify predetermined epitopes using a N2 domain-tagged antigen for screening on the antibody recombinant polypeptide. The current invention couples an additional domain to the antibody recombinant polypeptide without the antigen-tag in screening potential antigen-antibody binding in the phage system.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jacob Cheu whose telephone number is 571-272-0814. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jacob Cheu
Examiner
Art Unit 1641

April 7, 2006

LONG V. LE
SUPERVISORY PATENT EXAMINER
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04/17/06